



Account / Revue

Dendrimers and macrocycles: Reciprocal influence on the properties

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Dedicated to the Memory of Prof. Pierre-Gilles de Gennes.

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Abstract

The various types of dendritic compounds incorporating macrocycle(s) in some part(s) of their molecular architectures are described. As an illustration of such compounds, emphasis is put on those based on phosphorus derivatives. The type and location of the macrocycle(s) in the dendrimer are varied: crown ethers as end groups or as pendant internal groups, tetraazamacrocycles or triazatriolefinic macrocycles as end groups, a phosphorus-containing macrocycle or a phthalocyanine as core. The influence of the dendritic structure on the macrocycle, and conversely of the macrocycle(s) on the dendritic structure is demonstrated in several cases. Some of these compounds possess original properties, such as the detection of diastereoisomers by NMR, the detection of barium salts by electrochemistry, an enhanced fluorescence useful in biological experiments, an increased stability for nanolatexes, or the elaboration of Pd nanoparticles having a catalytic activity. *To cite this article: A.-M. Caminade et al., C. R. Chimie 12 (2009).*

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Résumé

Les différents types de composés dendritiques incorporant un ou des macrocycle(s) dans certaines parties de leur architecture moléculaire sont décrits. Pour illustrer ce type de composés, ceux basés sur des dérivés phosphorés sont particulièrement mis en lumière. Le type et la localisation des macrocycles dans le dendrimère sont variés: des éthers couronnes en surface ou en tant que groupes pendants à l'intérieur, des tétraazamacrocycles ou des triazatrioléfiniques macrocycliques en tant que groupes terminaux, un macrocycle phosphoré ou une phthalocyanine au cœur. L'influence de la structure dendritique sur le macrocycle, et inversement du macrocycle sur la structure dendritique sont démontrées dans plusieurs cas. Certains de ces composés possèdent des propriétés originales telles la détection de diastéréoisomères par RMN ou de sels de baryum par électrochimie, une augmentation de la fluorescence utile en biologie, un accroissement de la stabilité de nanolatex, ou l'élaboration de nanoparticules de Pd ayant une activité catalytique. *Pour citer cet article : A.-M. Caminade et al., C. R. Chimie 12 (2009).*

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Keywords: Dendrimers; Macrocycles; Nanosciences; Hyperbranched polymers; Phosphorus; Complexation

Mots-clés: Dendrimères ; Macrocycles ; Nanosciences ; Polymères hyperramifiés ; Phosphore ; Complexation

1. Introduction

Dendrimers [1] undoubtedly constitute one of the major fields of research connecting chemistry to nanosciences, with more than 1000 publications and more than 100 patents per year since five years. These very special types of polymers, hyperbranched and multifunctional, elaborated step by step (generation after generation), constitute a particular example of “soft matter” [2]. Thanks to the numerous properties they possess in various fields such as catalysis, materials and biology, interest in dendrimers is continuously growing each year. Macrocycles [3] are another type of macromolecules that have also attracted the attention

of researchers in different fields for several decades now. Combination of both types of macromolecules is supposed to increase the level of preorganization and might induce cooperative effects affording specific properties different from those produced by the separated parts [4]. The first example in this field dates back to 1992 [5]; it concerned a dendrimer bearing azacrown ether macrocycles as constituents of each branch (type **A** in Fig. 1). Such types of dendritic architectures are still relatively rare, but other types of dendrimers functionalized by crown ethers at some of the internal layers (type **B**) [6], or at each layer [5,7] have also been synthesized, affording brilliant skills as electron carriers. Other structures comprising

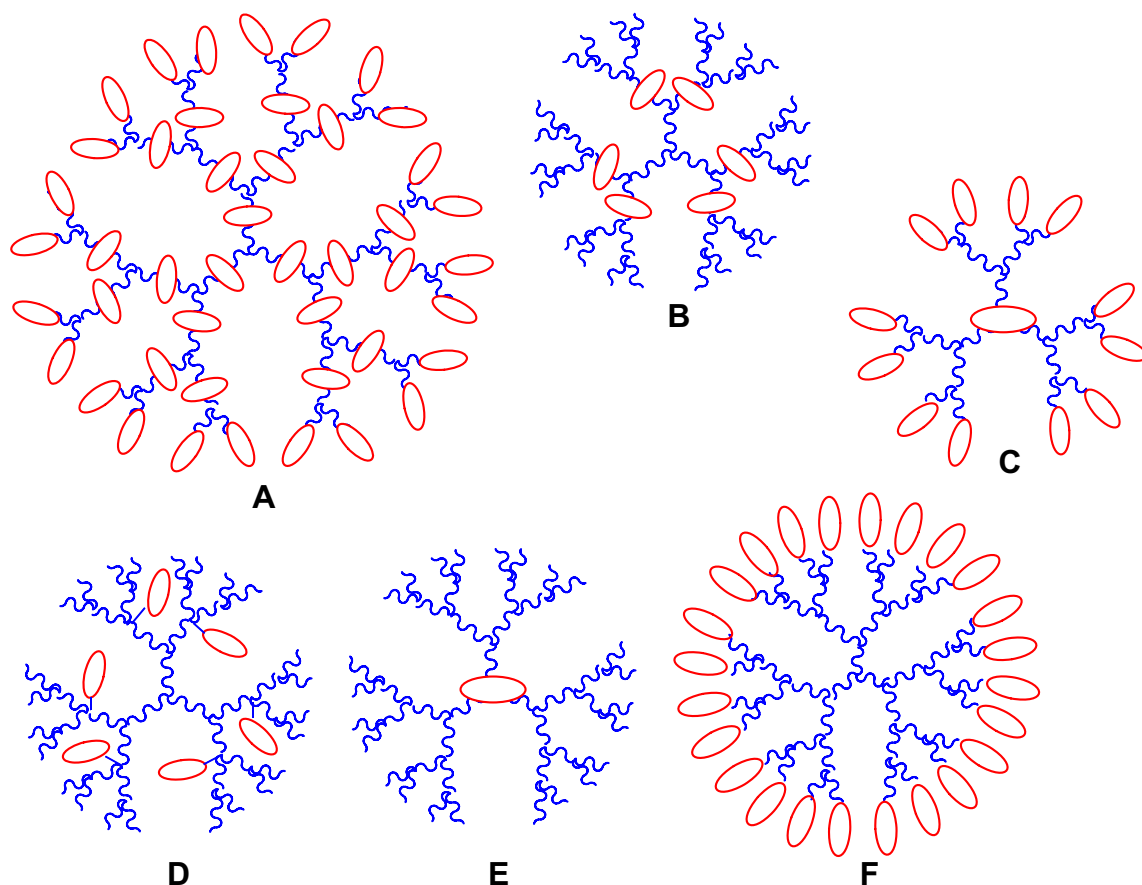
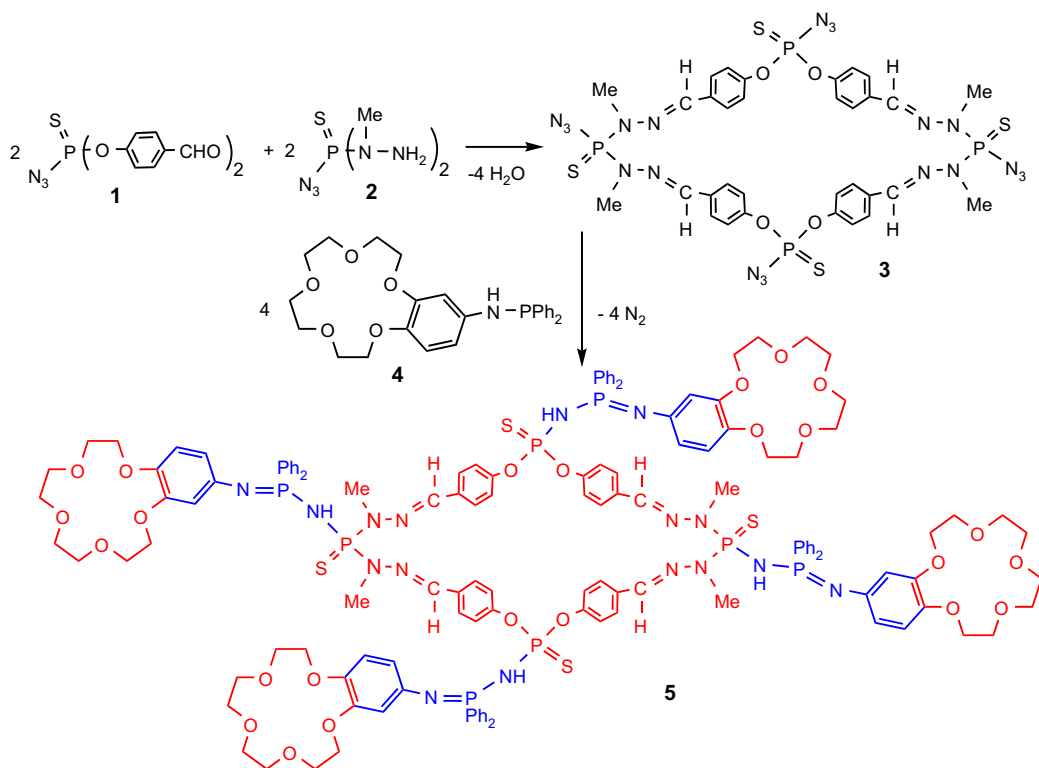


Fig. 1. Schematized types of molecular architectures possessing both macrocycles and dendritic branches.

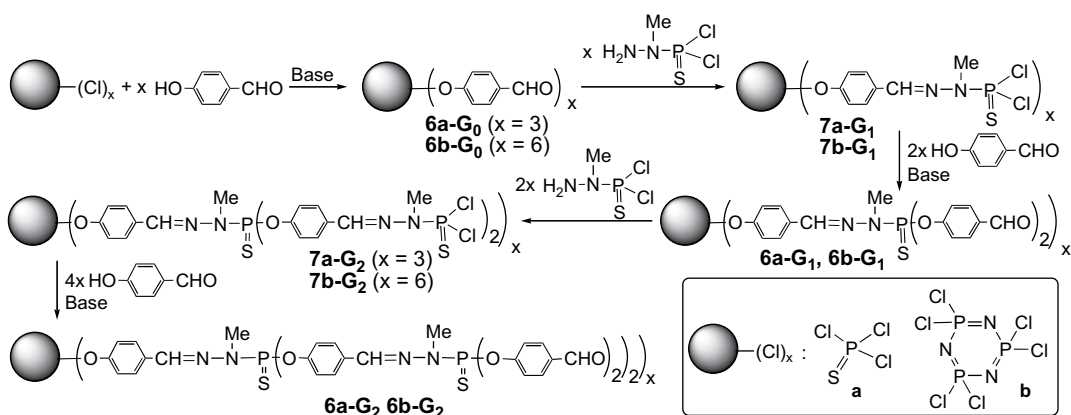


Scheme 1. Synthesis of a compound possessing five macrocycles.

a combination of porphyrins at each layer of the dendrimers have light-harvesting properties [8], whereas a dendrimer possessing azithia macrocycles at each layer was able to complex palladium [9].

However, the largest number of dendritic structures connected to macrocycles possesses a macrocycle as core (type **E**, Fig. 1). Porphyrins [10], phthalocyanines [11], cyclams [12], or crown ethers [13], are the types

of macrocycles the most widely used for this purpose. A shielding effect of the branches towards the core is generally expected. Dendrimers bearing macrocycles at the periphery are also well known in the literature even though less examples are described than for the macrocycle at the core. It is believed that increasing the number of macrocycles in a single molecule could enhance the properties of such assemblies (type **F**).

Scheme 2. Main method of synthesis of phosphorus-containing dendrimers, starting from either $\text{P}(\text{S})\text{Cl}_3$ or $\text{N}_3\text{P}_3\text{Cl}_6$ as core.

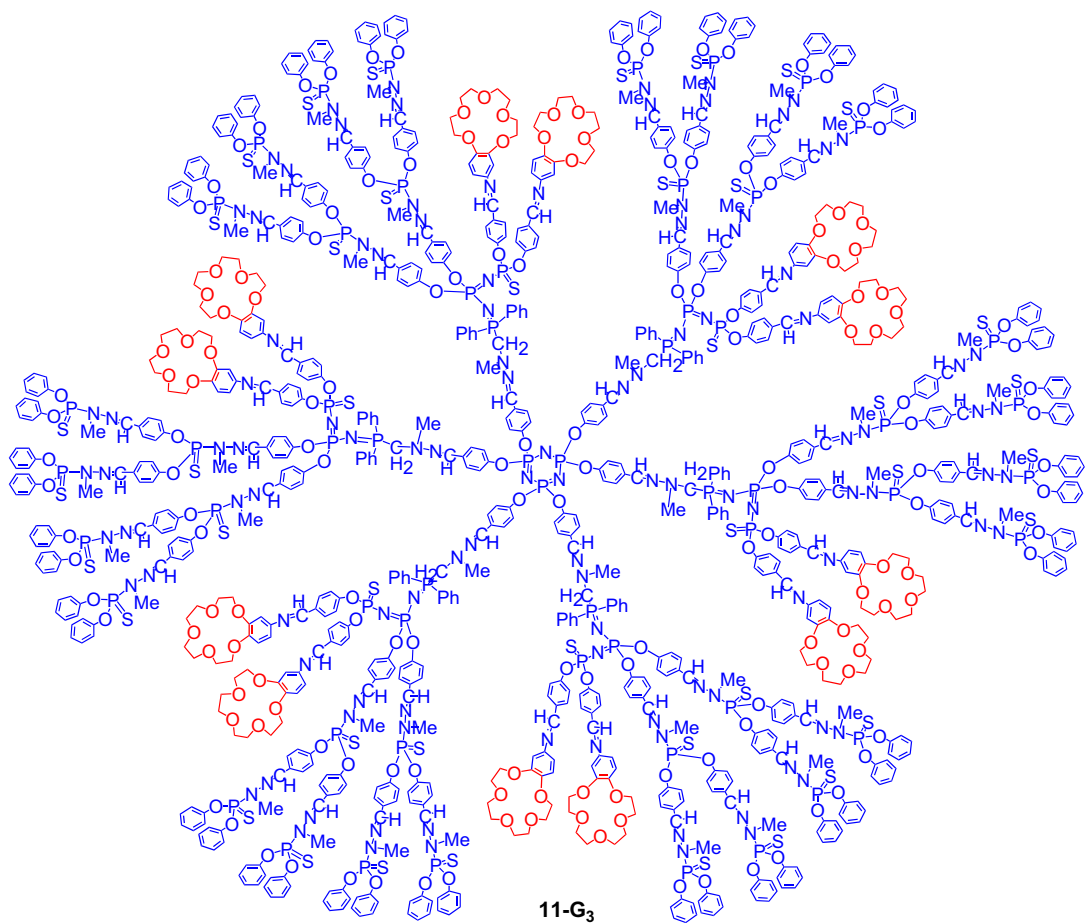


Fig. 2. Expanded structure of the unique example of a dendrimer possessing macrocycles linked to the internal branches (type **D** of Fig. 1).

Examples with porphyrins [14] and phthalocyanines [15] as peripheral substituents were in particular reported. Fig. 1 displays the various types of molecular architectures connecting macrocycles to dendrimers that have been synthesized up to now. As indicated above, the largest number of examples known to date pertains to types **E** and **F**.

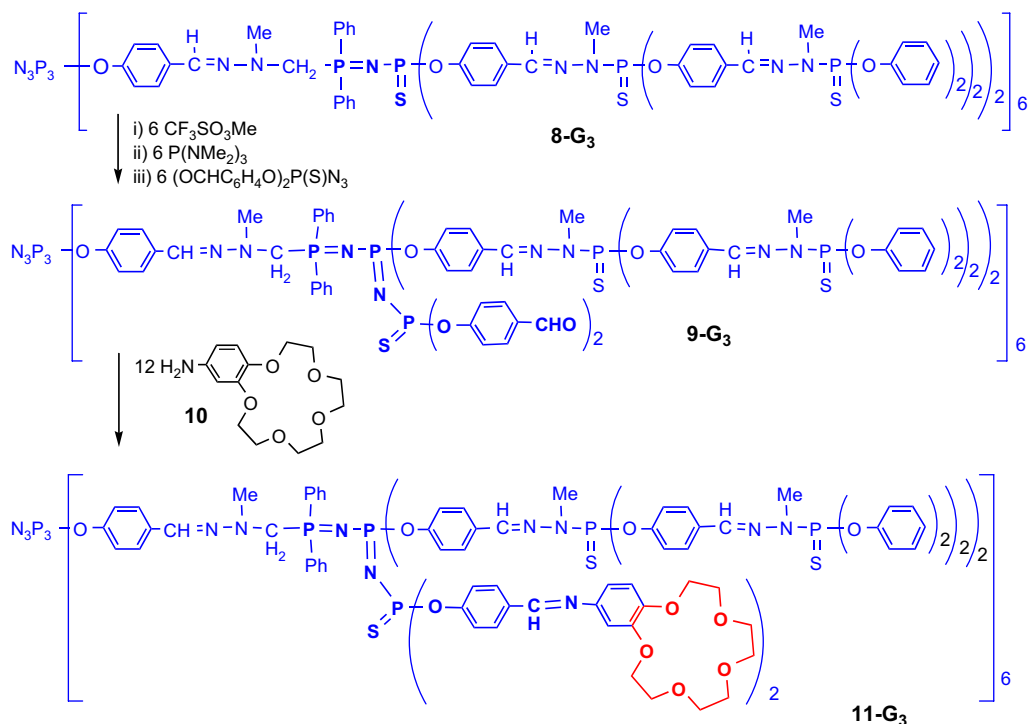
In this account, we will describe the specific contribution of phosphorus-containing dendrimers to this field of research. Depending on the location and the type of macrocycles, these compounds possess various properties and uses that will be also described.

2. Synthesis and properties of phosphorus dendrimers including macrocycles

We have a longstanding interest and experience in the synthesis and study of properties of phosphorus-containing macrocycles [16] and dendrimers [17], and

we tried very early to combine both types of compounds. The first example of such combination concerns a compound possessing a central macrocycle, functionalized by four linkers bearing at their end another type of macrocycle [18]. The central macrocycle is synthesized using our classical [2 + 2] condensation method between two equivalents of a dialdehyde such as **1** and two equivalents of a phosphodihydrazide such as **2**, to afford the 36-membered ring **3**. The presence of four azide groups allows performing Staudinger reactions with four equivalents of the phosphine **4** bearing a crown ether. The multi-macrocyclic species **5** obtained after a spontaneous rearrangement contains one phosphorus macrocycle at the core and four crown ether macrocycles on the periphery, linked by PNPS linkages, which also constitute the branches of several types of our phosphorus-containing dendrimers [19].

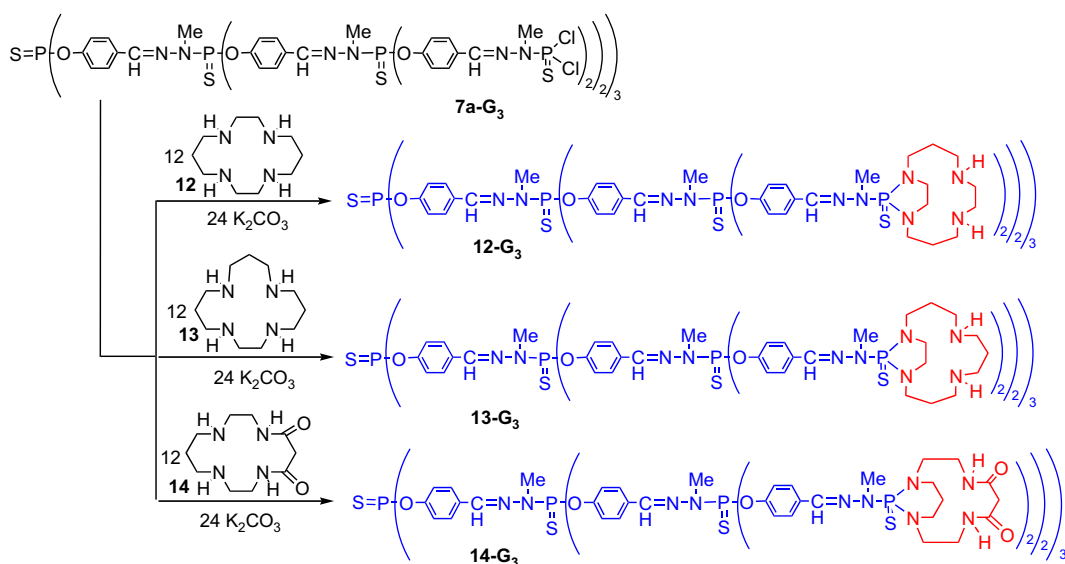
This first example pertains to the type **C** of Fig. 1, which is relatively rare, but we have also described



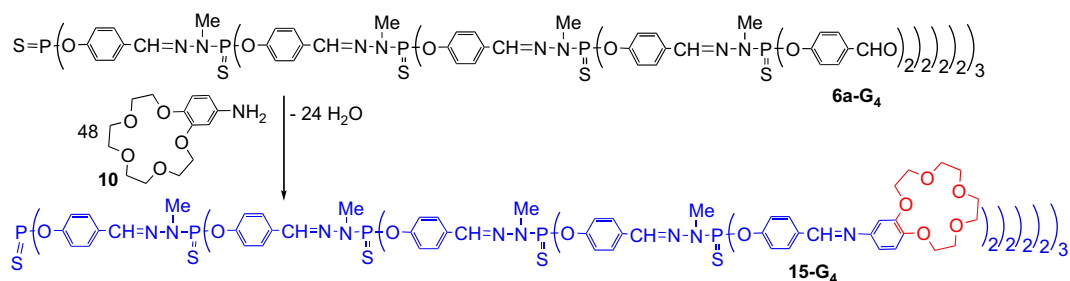
Scheme 3. Synthesis of a dendrimer incorporating 12 crown ethers in its internal structure.

a very original example of type **D** compound; such compound is the only example ever described to date for any type of dendrimers in which macrocycles are linked to the internal branches, but do not pertain to the branches.

Our main method of synthesis of dendrimers consists in the repetition of substitution reactions of 4-hydroxybenzaldehyde in basic conditions on PCl₂ end groups, followed by the condensation reaction of the aldehydes by the phosphorhydrazide H₂NNMeP(S)Cl₂,



Scheme 4. Grafting of various tetraazamacrocycles on the surface of third generation dendrimers.



Scheme 5. Grafting of crown ethers to the surface of a fourth generation dendrimer.

starting from either $P(S)Cl_3$ (**a** series) [17] or $N_3P_3Cl_6$ (**b** series) [20] as core (Scheme 2). Each time these two steps are repeated a new generation is created (the generation number is noted n). Depending on the step considered, these dendrimers are terminated either by aldehydes (series **6-G_n**) or by $P(S)Cl_2$ groups (series **7-G_n**), both being particularly suitable for further functionalizations to afford the desired properties [21].

This method is very powerful (both steps are quantitative) and allows numerous changes. For instance, to obtain the compound of type **D** shown in Fig. 2, a dendrimer possessing $P=N-P=S$ linkages in the internal structure such as **8-G₃** must be first synthesized. This linkage [19] is obtained by Staudinger reactions used as one alternative step during our classical synthetic process; it is able to undergo a selective alkylation on sulphur, which induces a weakening of the phosphorus sulphur bond. Using a nucleophilic phosphine such as $P(NMe_2)_3$ induces a desulphurization and affords tricoordinated phosphorus atoms inside the structure. These P^{III} are able to undergo a Staudinger reaction, in particular with a phosphorus azide linked to two aldehydes, to afford compound **9-G₃** [22]. The presence of internal aldehydes allowed the development of a large number of reactions [23], in particular the condensation with 4-aminobenzo-15-crown-5 **10**, to afford the very special dendritic species **11-G₃** (Scheme 3, Fig. 2) [24].

Dendrimer **11-G₃** demonstrates that the art of synthesis of dendritic molecules can attain a high degree of sophistication, but in most cases we have synthesized simpler dendritic compounds bearing macrocycles either at the periphery (type **F**) or at the core (type **E**, Fig. 1).

2.1. Macrocycles at the periphery of phosphorus dendrimers

We have described the synthesis of type **F** dendritic structures starting from either $P(S)Cl_2$ functions or

aldehydes, that are the classical functional terminal groups in our main method of synthesis of dendrimers (see Scheme 2).

We have already shown that the $P(S)Cl_2$ terminal groups of dendrimers **7a-G_n** are able to react with primary and secondary amines [25]. By treating dendrimers **7a-G_n** (up to generation 3) with three types of macrocycles 1,4,8,11-tetraazacyclotetradecane (cyclam, **12**), 1,4,8,12-tetraazacyclopentadecane (**13**), and 1,4,8,11-tetraazacyclotetradecane-5,7-dione (**14**) in the presence of K_2CO_3 , we might expect either the grafting of one or two macrocycles per $P(S)Cl_2$. In the case of a single macrocycle, the grafting can lead either to 5-membered rings (diazaphospholanes) or 6-membered rings (diazaphosphorinanes) starting from **12** and **13**, whereas only 6-membered rings can be obtained in the case of **14**, due to the known low reactivity of the amides. In fact, in all cases, only one macrocycle is grafted per $P(S)Cl_2$ group. More surprisingly, the reaction of macrocycles **12** and **13** is highly regiospecific, and only 5-membered heterocycles are created in both cases, leading to dendrimers **12-G_n** and **13-G_n** ($n=0-3$); 6-membered heterocycles are obtained as expected in the case of **14**, leading to dendrimers **14-G_n** (Scheme 4) [26].

Starting from the aldehyde terminal groups, the simplest way to graft macrocycles consists in condensation reactions with macrocycles functionalized by an amine. For instance, condensation reactions between the aldehyde groups of dendrimers **6a-G_n** (generations 1–4) and 6–48 equivalents of the amino crown ether **10** afford dendrimers **15-G_n**, capped by the crown ethers (Scheme 5) [27]. Such bulky substituents necessitate a prolonged time of reaction; completion of the condensations is accomplished within 1 week for the first generation, but necessitates 3 weeks for the fourth generation. Remarkably, terminal crown ethers act as a shield against hydrolysis: the imine functions remain intact after stirring compound **15-G₄** for 48 h in a THF/water (80:20) solution. The second generation,

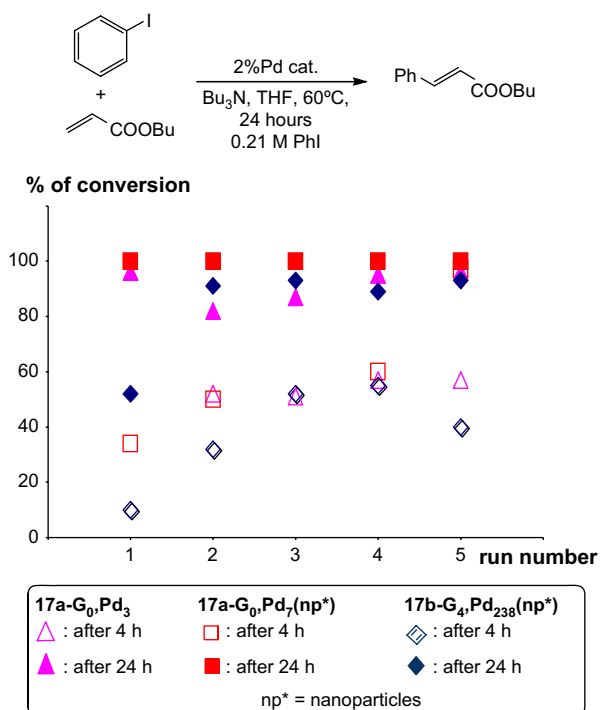


Fig. 3. Percentage of conversion in the Heck reaction shown above after 4 h (hollow marks) and after 24 h (plain marks) using 2% of Pd catalyst (either the discrete Pd complex [17a-G₀, Pd₃] (triangles) or the Pd nanoparticle complexes [17a-G₀, Pd₇] (squares) or the Pd nanoparticle complexes [17b-G₄, Pd₂₃₈] (rhombus)). After the initial run (number 1), all catalytic samples were reused four times (runs 2–5).

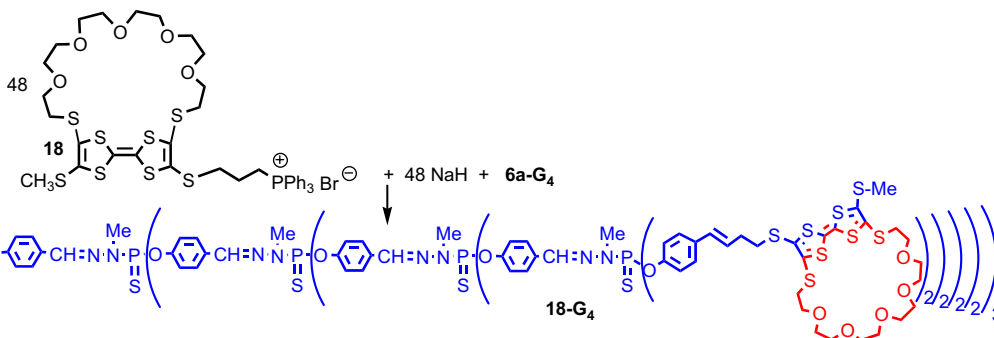
Pd⁰. Depending on both the source of palladium and the nature of the dendritic species (core, generation, substituents of the macrocycles), either discrete palladium complexes or nanoparticles are obtained. A cooperative effect is observed in the case of the fourth generation. Indeed, the ratio macrocycle/Pd can be deduced from elemental analyses: the ratio is 2.4 macrocycle/Pd with the first generation (17b-G₁)

whereas it is 0.4 macrocycle/Pd with the fourth generation (17b-G₄). These nanoparticles have generally a small size (diameters from 2.4 to 5.7 nm), and a narrow size distribution (± 1.0 nm). The catalytic properties of the discrete complexes and of nanoparticles elaborated with dendrimers from generation 0 and 4 were tested in Heck reactions. As shown in Fig. 3, in the initial experiments (run 1), the worst results are obtained with the nanoparticles obtained with the fourth generation dendrimer. Recycling experiments were carried out four times in all cases. Surprisingly, the efficiency is improved when the number of recycling is increased. This improvement could be explained by a decrease in the size of the nanoparticles observed by comparing the TEM images obtained initially and after the fifth run [28].

Other types of reactions can be applied to aldehyde terminal groups, and particularly Wittig reactions. The macrocyclic TTF derivative **18** reacts with dendrimer **6a-G₄**, to afford the fourth generation dendrimer **18-G₄** (Scheme 7). This very special macrocyclic dendritic system is able to respond electrochemically, especially when interacting with a guest ion, and is potentially usable as chemosensor. The electrooxidation of dendrimers **18-G_n** compares well with that of the monomeric species, whereas the electrodeposition onto the electrode is favoured with the highest generations. The most remarkable feature of these dendrimer films is their unique capacity to control the complexation/expulsion properties of Ba²⁺ cations. Fig. 4 shows the electrochemical response of the electrode modified by dendrimer **18-G₄** when increasing quantities of barium are added [30].

2.2. Macrocycle at the core of phosphorus dendrimers

Two different strategies can be envisaged to obtain a dendrimer possessing a macrocycle as core (type **E** in



Scheme 7. Wittig reactions for the grafting of TTF-crown ether derivatives on the surface of a fourth generation dendrimer.

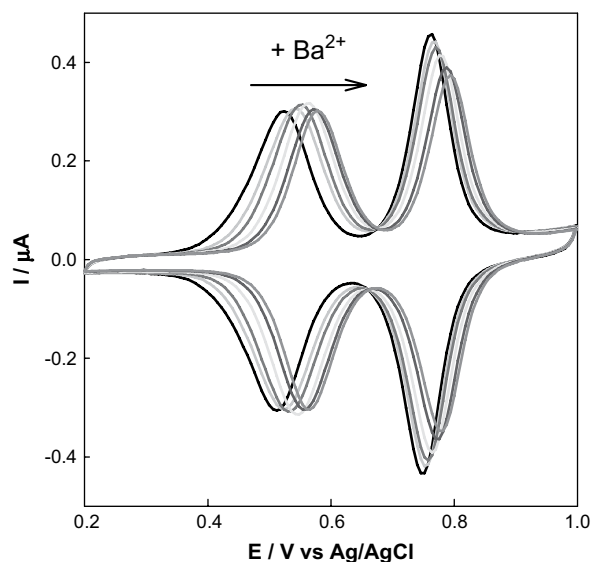
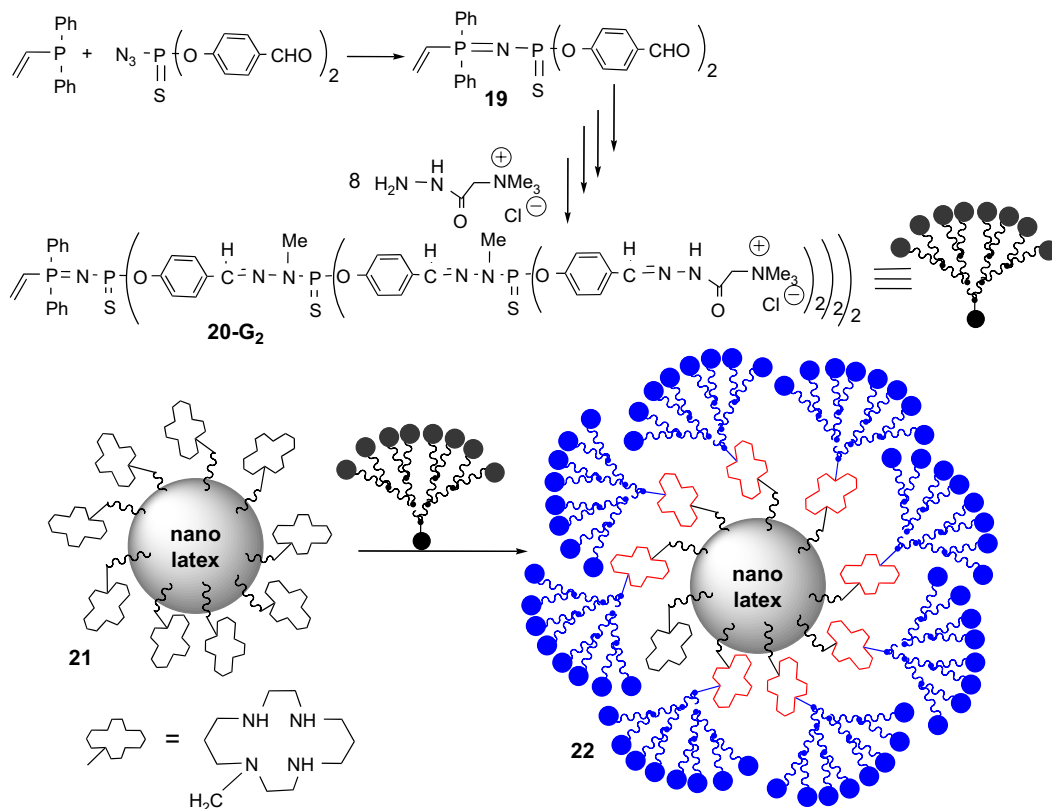


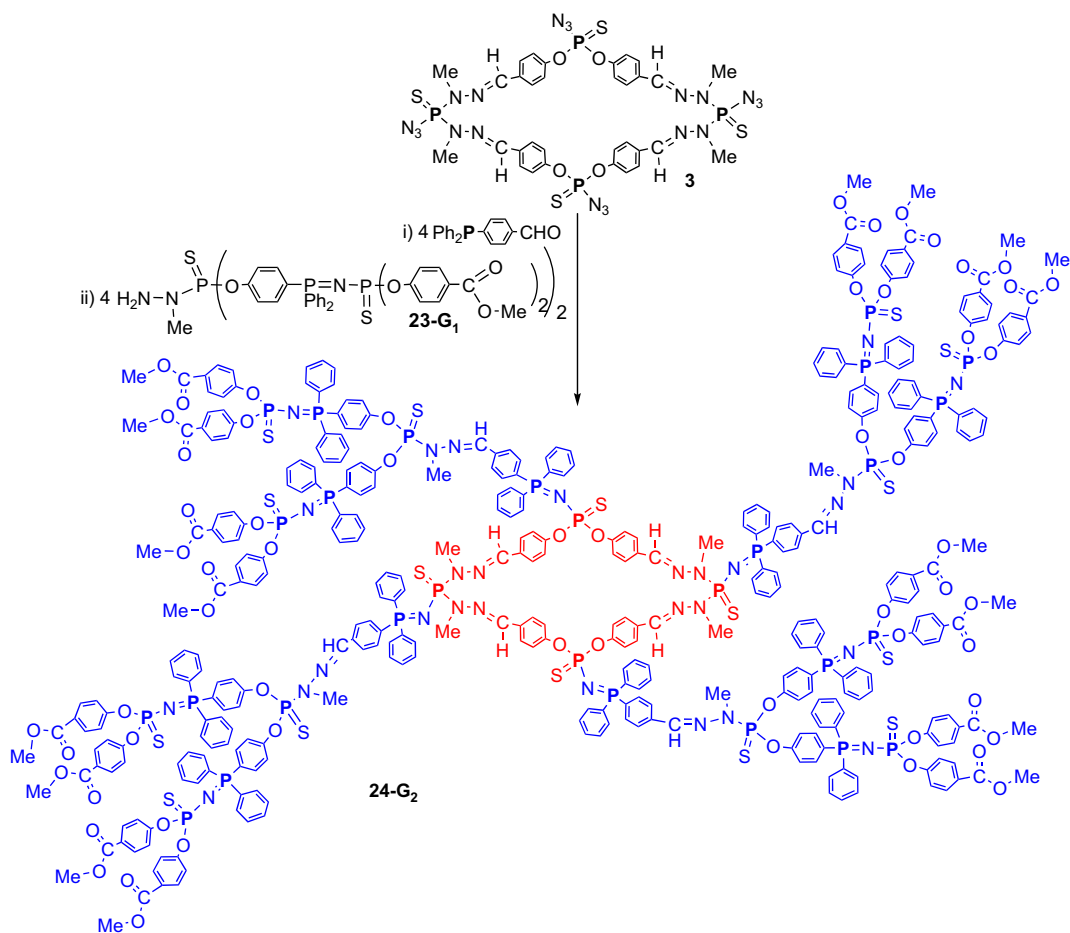
Fig. 4. Modification of the electrochemical response of an electrode covered by electrodeposition of dendrimer **18-G₄**, when exposed to increasing amounts of Ba^{2+} .

Fig. 1): either the classical method of synthesis of dendrimers is applied starting from this particular core or dendrons are grafted to the macrocycle in the final step. Dendrons, also called dendritic wedges, are a special type of dendritic molecules possessing one functional and reactive group at the core, besides the functional groups located at the surface, and are particularly useful to build sophisticated dendritic architectures [31]. We have in particular synthesized a series of dendrons possessing an activated vinyl group at the core, elaborated from vinyl phosphine, and grown using the method of synthesis shown in Scheme 2; these dendrons are able to react with primary and secondary amines in Michael type additions [32]. One example of such dendrons (**20-G₂**) is shown in Scheme 8.

Aqueous suspensions of polymer nanoparticles, also called nanolatexes have a potential wide range of applications, due in particular to their high surface-to-volume ratio. Thus, improved stability and tailored functionalities are a challenging endeavour. Polycationic dendrons of type **20-G_n** ($n = 0, 1, 2$) react



Scheme 8. Grafting of dendrons by their core to a nanolatex functionalized by cyclams. The dendron **20-G₂** was elaborated from compound **19**, by using the method shown in Scheme 2, followed by the condensation of the Girard T reagent to the surface in the last step.

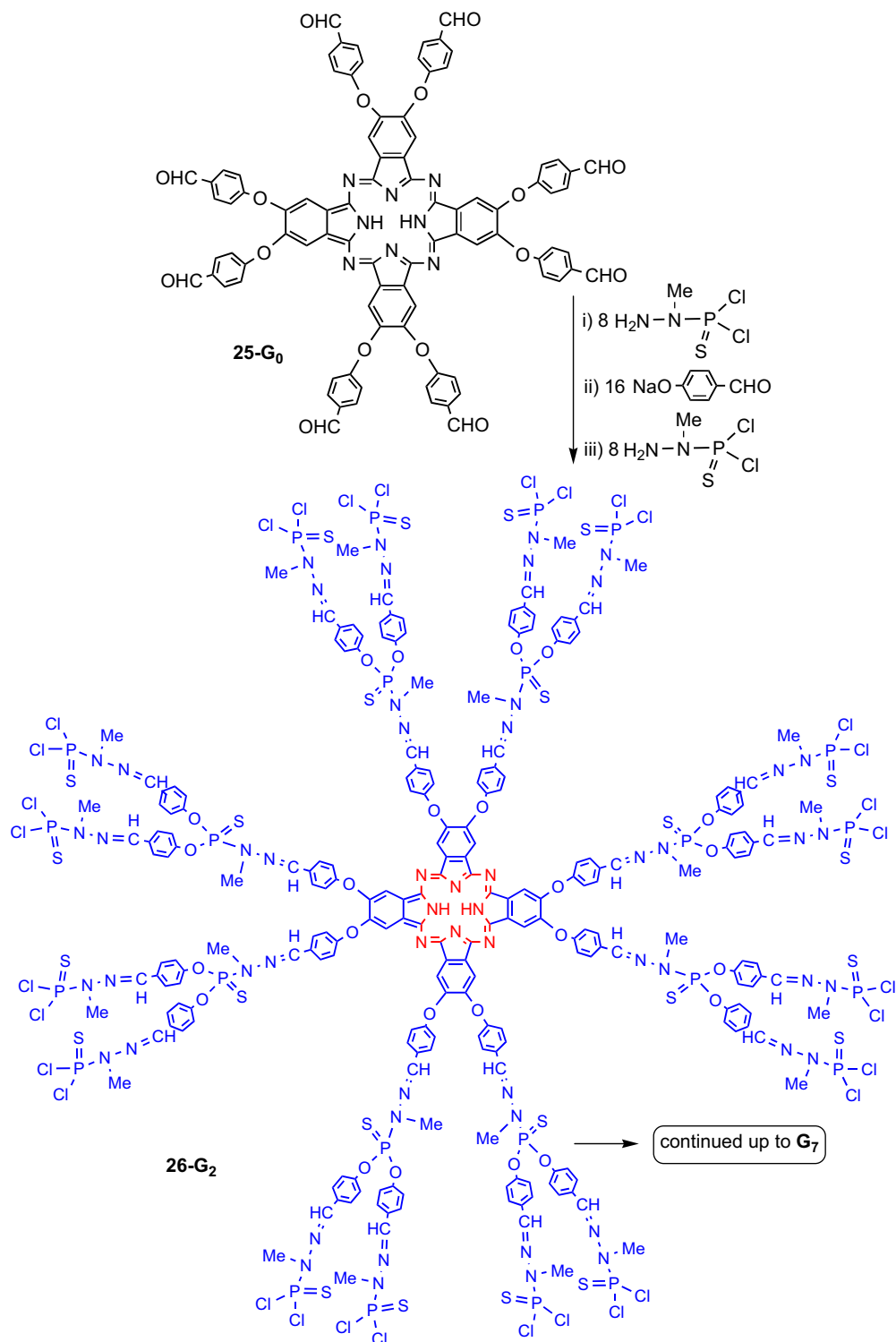


Scheme 9. Grafting of four dendrons by their core to a 36-membered tetrafunctional macrocycle.

readily with the cyclam linked to the surface of nanolatexes (**21**, diameter 16 nm) (Scheme 8). Remarkably, the number of dendrons linked to the nanolatex depends on the generation (300 **20-G₀**, or 150 **20-G₁** or 90 **20-G₂**), whereas the number of cations per nanolatex is almost constant (600–800 ammonium groups per particle, whatever the generation used). In all cases, an improved stability of the aqueous suspension is observed, as well as an increased thermal stability. Furthermore, despite the presence of the dendritic layer, the macrocycles at the core retain their metal-complexing ability, with a Cu(II) binding capacity of 0.2 mmol/g of nanoparticle, demonstrating the permeability of the dendritic shell [33].

Another example of grafting dendrons to a macrocycle allowed us to demonstrate for the first time the properties of dendrons as topological amplifiers. Indeed, even if the presence of diastereoisomers in macrocycle **3** (synthesized in Scheme 1) could be anticipated, with the zero value found for its optical

rotation strongly suggesting a 50:50 ratio for the stereoisomers on each phosphorus atom, the existence of such diastereoisomers was never detected previously. Even the grafting of hindered but small substituents did not allow to detect any trace of diastereoisomers. On the other hand, the grafting of dendrons through a Staudinger reaction with Ph₂PC₆H₄CHO followed by condensation reactions with the core of dendron **23-G₁** affords the dendrimer **24-G₂** (Scheme 9). The ³¹P NMR spectrum of this compound gives sharp signals for the phosphorus atoms pertaining to the dendrons, but multiple signals for the P=N–P=S linkages directly linked to the macrocycle, instead of the doublets observed with smaller substituents. The minimization of interactions between the end groups of the dendrons necessitates modification of the angles at the level of their roots, differently depending on the diastereoisomers to which they are linked. Since it is known that ³¹P NMR chemical shifts are very sensitive to modification of the



Scheme 10. First steps of the synthesis of the series of dendrimers possessing a phthalocyanine as core. The synthesis has been carried out up to the seventh generation, using the method of synthesis shown in Scheme 2. Compounds $25-G_n$ have aldehyde end groups, compounds $26-G_n$ have $P(S)Cl_2$ end groups.

angles around phosphorus, one may attribute the phenomenon observed here to diastereoisomers, demonstrating as expected the role of dendrons as amplifiers of local phenomena [34].

The second strategy usable to obtain dendrimers possessing a macrocycle as core necessitates a multi-functional macrocycle, whose functions are compatible with our classical method of synthesis of dendrimers shown in Scheme 2. The phthalocyanine **25-G₀** possesses eight aldehyde groups, thus it is perfectly suitable to react first with the phosphorhydrazide $\text{H}_2\text{NNMeP(S)Cl}_2$, then with hydroxybenzaldehyde in basic conditions, and to repeat several times both steps to continue the growing to afford dendrimers **25-G_n** (CHO terminal groups) and dendrimers **26-G_n** (P(S)Cl₂ terminal groups) (Scheme 10) [35].

The phthalocyanine at the core is usable as a sensor and a probe for determining the properties of the internal structure and the reciprocal influence of the core, branches and surface on the whole structure. Indeed, the UV–vis spectra display both a hyperchromic effect (exaltation of the intensity, due to an increased isolation) and a bathochromic effect (displacement of the wavelength towards the red) on the Q-bands with increasing generations, as well as the disappearance of aggregation phenomena (Fig. 5). Depending on the solvents used these phenomena are more or less pronounced and allowed to demonstrate that the influence of the dendritic branches upon the core mimics a highly polar solvent such as DMF. Measurement of the fluorescence quantum yield shows that it is higher for **25-G₃** and **25-G₄** than for **25-G₀**, illustrating an increased site isolation. However, the core remains accessible in all cases, as shown by the addition of NaOH, which induces a dramatic diminishing of the fluorescence intensity, due to the chemical

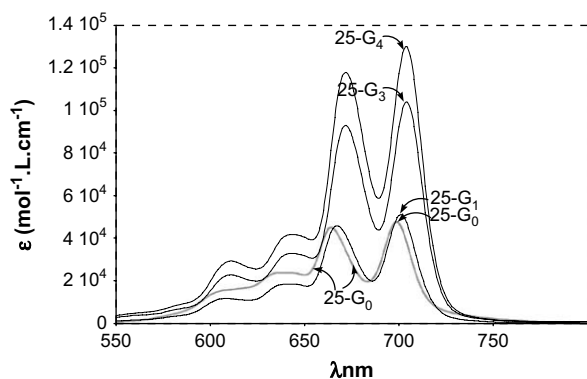


Fig. 5. Evolution of the Q-bands of dendrimers **25-G_n** with the generation.

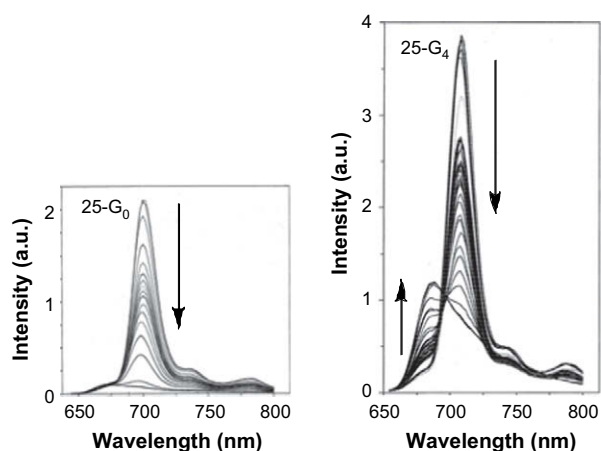


Fig. 6. Variation of the fluorescence spectra of the generations zero and four of the dendrimers **25-G_n** upon addition of NaOH, which induces a diminishing of the band intensity.

modification of the core when it becomes dianionic with a modified geometry (from D_{2h} for the neutral form to D_{4h} for the dianionic form) (Fig. 6) [35]. The phthalocyanine can also be used to trap metals, in particular copper and cobalt cations. In both cases, the presence of a paramagnetic metal at the core perturbs the NMR response not only of the core but also of the branches at least for the first generations. Furthermore, the total disappearance of the fluorescence upon complexation is observed for all generations [36].

The fifth generation of the dendrimers possessing a phthalocyanine as core has been functionalized by ammonium terminal groups, directly obtained by the reaction of $\text{NH}_2\text{CH}_2\text{CH}_2\text{NEt}_2$ with the P(S)Cl₂ terminal groups of dendrimer **26-G₅**. This diamine ensures the solubility in water of dendrimers capped by these groups, very useful for various applications related to material science and biology [37]. The grafting of these ammonium groups to **26-G₅** affords compound **27-G₅** (Fig. 7), which possesses very original properties at the nanometric level. Surprisingly, the presence of a hydrophobic interior and a hydrophilic surface afford in the UV–vis spectra in water the Q-bands characteristic of a phthalocyanine in the solid state. Furthermore, only the signals corresponding to the ethyl (external) groups are detected by ¹H NMR, also in water. Both phenomena evoke a frozen internal structure surrounded by solubilizing functions, reminiscent of a solid colloidal state in solution. A progressive addition of THF to the aqueous solution indicates a progressive solubilization of the core, shown by a sharpening of the signals of the Q-band in the UV–vis spectra, and the re-appearance of all the

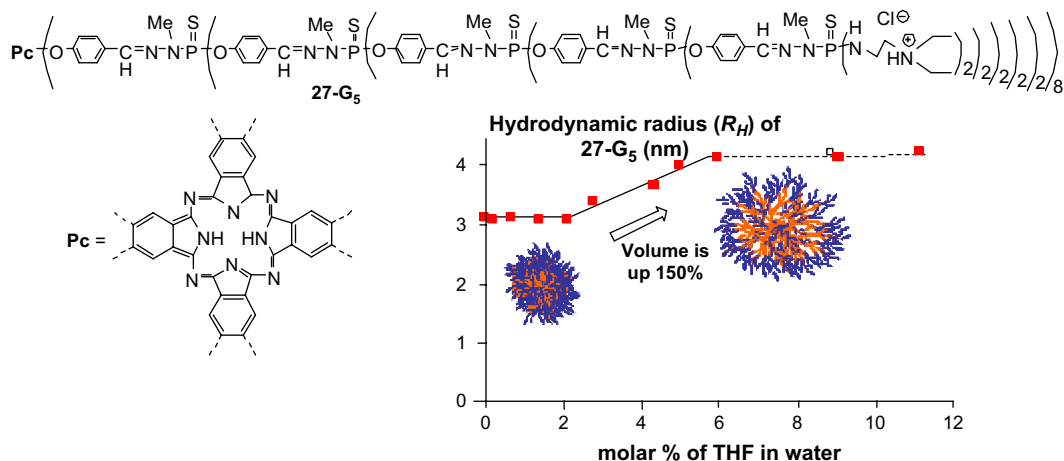


Fig. 7. Variation of the hydrodynamic radius of the water-soluble dendrimer **27-G₅** in water with increasing amounts of THF measured by diffusion NMR, and “artist” view of the swelling and blooming phenomena.

signals of the internal layers in ¹H NMR. Diffusion measurements by pulsed-field gradient spin-echo NMR allowed us to deduce the variation of the hydrodynamic radius, which displays a dramatic increase when adding THF, as shown in Fig. 7. In view of these modifications, the internal structure of **27-G₅** could act as a nanosponge for lipophilic drugs; we have observed this phenomenon by ¹H NMR for the inclusion of tetramethylsilane (TMS). The increase of the volume has also unexpected macroscopic consequences on the viscosity of mixtures water/THF, with **27-G₅** acting as a buffer for regulating the viscosity [38].

As indicated above, water-soluble dendrimers may have interesting biological properties. Compound **27-G₅** shows rather moderate cytotoxicity towards Human epithelioid cervical carcinoma cells (HeLa), Human transformed primary Embryonic Kidney cells (HEK 293), and Human Umbilical Vein Endothelial Cells (HUVEC), generally lower than with lipofectin. For instance, the percentage of living HUVEC cells after 48 h in the presence of 10 μg/mL of lipofectin or **27-G₅** is *ca.* 70 and 90%, respectively. Furthermore, this compound is able to act as transfection agent, to deliver fluorescein-labeled oligodeoxyribonucleotide into HeLa cells. The presence of the phthalocyanine as core allowed us to detect the penetration inside the cells, detected by UV-induced fluorescence. The image by fluorescence microscope (Fig. 8) shows that the dendrimer alone is efficiently taken by the HUVEC cells [39], presumably via an endosomal uptake [40].

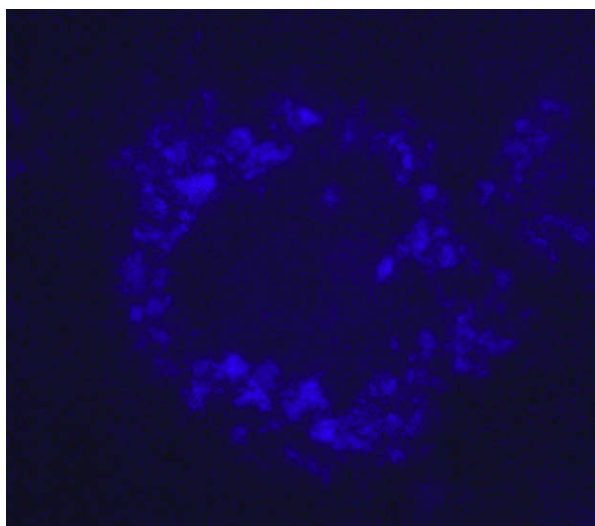


Fig. 8. The effect of incubation for 18 h of dendrimer **27-[G₅]** with HUVEC cells in the presence of serum, detected by fluorescence microscopy.

3. Conclusion

In this short review, we have shown that molecular design has allowed the synthesis of compounds possessing macrocycles in various parts of dendritic structures, particularly in the case of phosphorus derivatives. Some of these structures, the most original, are only obtainable up to date using the chemistry of phosphorus. If the design of such compounds was made in some cases mainly for aesthetic purposes, it turned out that most of these compounds possess original and interesting properties, arising from the presence of both the macrocyclic and the dendritic parts. The reciprocal influence of both components is particularly obvious when the macrocycle (especially a phthalocyanine) is used as core of the

dendrimer. Indeed, the branches act as a shield, preventing in particular aggregation, and partially protecting the core against water, both effects favouring an increased fluorescence, useful when using it as fluorescent probe for biological properties. On the other hand, the presence of a paramagnetic metal trapped by the core disturbs the NMR response of the whole dendritic structure. The presence of a large number of macrocycles on the surface of a dendrimer induces cooperative effects, demonstrated in particular in the case of dendrimers possessing triolefinic triazamacrocycles as terminal groups. Indeed, the stabilization of Pd nanoparticles necessitates a lower number of macrocycles (six times less) when they are connected to a fourth generation than when they are connected to a first generation. All these findings illustrate the highly specific properties of compounds combining these two types of entities (macrocycles and dendrimers) having so particular topologies. Future potential applications of such types of systems can be foreseen in the fields of catalysis, material science, and biology.

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